PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

In Re Application of:	)	
	)	
Sampson et al.	)	Group Art Unit: **1637**
	)	Examiner: **Chunduru, Suryaprabha**
Serial No.: **09/836,012**	)	
	)	Confirmation No. **6991**
Filed: **April 17, 2001**	)	
	)	
For: **METHOD AND REAGENTS FOR ANALYZING THE NUCLEOTIDE SEQUENCE OF NUCLEIC ACIDS**	)	Docket No.: **10992153-1 (050113-1220)**

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January 23, 2006

Belinda K. Weiss

Signature – Belinda Weiss

APPEAL BRIEF UNDER 37 C.F.R. §1.192

Mail Stop Appeal Brief - Patents
Commissioner of Patents and Trademarks
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

This is an appeal from the decision of Examiner Suryaprabha Chunduru, Group Art Unit 1637, mailed August 23, 2005, rejecting claims 1-17 and 74-83 in the present application and making the rejection FINAL.

It is not believed that extensions of time or fees are required to consider this Appeal Brief. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor are hereby authorized to be charged to Deposit Account No. 50-1078.

I. REAL PARTY IN INTEREST

The real party in interest of the instant application is Agilent Technologies, Inc.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF THE CLAIMS

Claims 1-17 and 74-83 are pending in the present application. Claims 18-73 have been cancelled.

IV. STATUS OF AMENDMENTS

No amendments have been made or requested since the mailing of the FINAL Office Action and all amendments submitted prior to the FINAL action have been entered. A copy of the current claims is attached hereto as Exhibit A.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention is directed to reagents and methods for recapitulating a target nucleic acid in the short-word form that can be analyzed by high-resolution mass spectrometry techniques. The methods and reagents utilize generic oligonucleotide precursor mixtures (X-mer precursor mixtures) comprising tags covalently attached through cleavable bonds, and enzymatic processes to alter the length, and concomitantly the mass, of only those X-mer precursors within a defined mixture that are complementary to the target nucleic acid and therefore have hybridized to the target nucleic acid to permit enzymatic processing. *Specification* at page 9, line 31 – page 10, line 6.

In one aspect, the present invention is a mixture or a set of sub-mixtures comprising nucleic acids and tags covalently attached to the nucleic acids through cleavable linkers for direct mass spectral analysis of the tags after release by cleavage of the linkers, where the tags are distinguishable by mass spectrometry and are assigned to known sequences of X-mer precursors. The mixture comprises X-mer precursors having a minimum length of 3 nucleotides. The minimum mixture coverage complexity (CC_M) of the mixture (or minimum composite mixture coverage complexity of the set of sub-mixtures) is 56 divided by N, where N is the number of distinct X-mers in the mixture. The length of the X-mer precursors can be selected independently for each X-mer precursor. Each of the X-mer precursors in the mixture is represented by a single chemical species. Each sub-mixture in the set has a reduced mixture coverage complexity relative to the composite mixture coverage complexity. Further, each sub-mixture comprises a plurality of X-mer precursors. *Specification* at page page 10, lines 7-19.

In another aspect, the present invention provides a method of analyzing a target nucleic acid sequence. In the method, a mixture of X-mer precursors (or a sub-mixture from a set of sub-mixtures) comprises tags covalently attached to the nucleic acids through cleavable linkers for direct mass spectral analysis of the tags after release by cleavage of the linkers, where the tags are distinguishable by mass spectrometry and are assigned to known sequences of X-mer precursors. The mixture comprises X-mer precursors having a minimum length of 3 nucleotides. The minimum mixture coverage complexity of the mixture (or minimum composite mixture coverage complexity of the set of sub-mixtures) is 56 divided by N, where N is the number of distinct X-mers in the mixture. The length of the X-mer precursors can be selected independently for each X-mer precursor. Each of the X-mer precursors in the mixture is represented by a single chemical species. Each sub-

mixture in the set has a reduced mixture coverage complexity relative to the composite mixture coverage complexity. Further, each sub-mixture comprises a plurality of X-mer precursors. *Specification* at page page 10, lines 20 – page 11, line 1.

The X-mer precursors in the mixture are hybridized to the target nucleic acid sequences producing hybrids. The hybrids are processed to alter the mass of the X-mer precursor portions of the hybrids in a target sequence-mediated reaction. The reaction captures hybridization events between X-mer precursors and their complementary sequences within a target nucleic acid by altering the mass of the X-mer precursor. As a result, sequence information on the target nucleic acids is recapitulated by the mass-altered X-mer precursors. Therefore, mass-altered X-mer precursors are then separated from the unaltered (i.e. unhybridized) X-mer precursors for analysis. *Specification* at page page 11, lines 2-9.

After separation, the tags are released from the mass-altered nucleic acid X-mer precursors by cleavage of the linkers. The isolated tags, which may be purified, are then analyzed by mass spectrometry. Additionally or alternatively, the step of cleaving the linkers and the step of analysis by mass spectrometry are performed in the same step. Since tags are assigned and linked to X-mer precursors whose nucleotide sequences are known, information obtained from mass spectral analysis is then used to determine the nucleotide sequence of the target nucleic acid. *Specification* at page page 11, lines 10-16.

In one embodiment, the present invention is a kit for carrying out the above method. The kit comprises a mixture or set of sub-mixtures as described above, an enzyme having DNA polymerase activity, and a multiplicity of chain-terminating nucleotide triphosphates. *Specification* at page page 11, lines 17-21.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 1-17 and 74-83 stand rejected as allegedly anticipated by *Southern et al.* in view of *Sorge*.

Claims 1, 3-6 and 74-80 stand rejected as allegedly obvious over the combination of *Brenner* in view of *Sorge*.

VII. ARGUMENT

(a) Rejection of Claims 1-17 and 74-83 over *Southern* in View of *Sorge*

Claims 1-17 and 74-83 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over *Southern et al.* (" *Southern*," WO 95/04160) in view of *Sorge* (" *Sorge*," U.S. Pat. No. 6,607,878). Applicants respectfully traverse this rejection.

As has been acknowledged by the Court of Appeals for the Federal Circuit, the U.S. Patent and Trademark Office (" USPTO") has the burden under section 103 to establish a *prima facie* case of obviousness by showing some objective teaching in the prior art or generally available knowledge of one of ordinary skill in the art that would lead that individual to the claimed invention. *See In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). The Manual of Patent Examining Procedure (MPEP) section 2143 discusses the requirements of a *prima facie* case for obviousness. That section provides as follows:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teaching. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and reasonable expectation of success must be found in the prior art, and not based on applicant's disclosure.

For at least the reasons set forth in more detail below, in the present case, when *Southern* and *Sorge* are combined they do not teach or suggest all of the features of at least the independent claims 1, 2, 7, 12, and 81-83.

In addition to the above-described defects of the rejection, Applicants respectfully assert that the proposed combination is improper. It has been well established that teachings of references can be combined only if there is some suggestion or incentive to do so. *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). Accordingly, there must be a teaching in the relevant art which would suggest to a person having ordinary skill in that art the desirability of combining the "ladder tag" design of *Southern*, where each discrete oligonucleotide sequence within the mixture is associated with a "spectrum" of mass entities, with the molecular weight "blocks" of colors or other tags of *Sorge*, where certain molecular weight ranges or "gaps" are reserved for post-digestion analysis. There is no teaching in either reference that would suggest the desirability of combining. Further, knowledge generally available in the art would not motivate one to combine the references. Here, the Office has used impermissible hindsight analysis and, with the invention of the claims in mind, have picked two isolated disclosures in the art and attempted to combine them when there is no motivation to do so. *See In re Fine* 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

Irrespective of the clear lack of motivation to combine the *Southern* and *Sorge* references, the rejection is improper. Even if the teachings of the two references are deemed by the Board to be properly combinable, such combination does not result in Applicants' claimed invention. As provided above, each of Applicants' independent claims recite the following:

> the mixture has a minimum mixture coverage complexity of at least 56/N or wherein the set of sub-mixtures has a composite mixture coverage

> complexity of at least 56/N, wherein N represents the number of distinct X-mer precursors in the mixture...
>
> any given oligonucleotide sequence in the mixture is attached to preferably a single tag with a discrete molecular weight.

(emphasis added). Instead of indicating where these distinct features are found in either of *Southern*'s or *Sorge*'s disclosures, the rejection simply generally references portions of *Southern* that refer to "a mixture of 4096 hexanucleotides." *Southern* does not teach or suggest a mixture or set of sub-mixtures of the independent claims that have the specific features quoted above.

Applicants have noted the following in the specification:

> As the average length of the X-mer precursor increases, the number of distinct X-mers in the mixtures of this invention also increases and the mixture coverage complexity may decrease. The lower limit of the mixture coverage complexity is equal to a value of 56 divided by the number of X-mers in the mixture. The length of the X-mer precursors can be selected independently for each X-mer precursor,

Specification at 29, lines 1-5. While certain embodiments of *Southern* may suggest mixtures that might possibly have this characteristic, *Southern* does not specifically teach or suggest mixtures of sub-mixtures of X-mers that have this feature. In that *Sorge* does not remedy this deficiency of the *Southern* reference, Applicants respectfully submit that independent claims 1, 2, 7, 12, and 81-83 are allowable over the *Southern/Sorge* combination.

In addition, the Office admits that *Southern* does " not specifically teach any oligonucleotide sequence in the mixture is attached to preferably a single tag with a discrete molecular weight, tags distinguishable by mass spectrometry and kit comprising said mixture of X-mer precursors." *Office Action* at 4, lines 3-5. Indeed, each X-mer precursor of the independent claims possesses a single mass, whereas each oligonucleotide in *Southern* is associated with spectra of masses that represent the nucleotide sequence of interest. *Sorge*

does not remedy this deficiency of the *Southern* reference either. As noted above, *Sorge* is not properly combinable with *Southern* for at least the reason that *Sorge* is directed to distinguishing fragments, obtained after enzyme cleavage, from one another " on the basis of color." *See, e.g., Sorge* at col. 22, lines 45-67. *See also Sorge* at col. 23, lines 12-16 (" the identity of a particular private nucleotide is associated with the color of a fluorescent tag associated with a particular pb primer. Four different colors could correspond with the four possible bases at a given private nucleotide position. Thus, the pa primer corresponding to each of the four possible nucleotides at a given private sequence position will be included in a separate vessel with a pb primer that includes a particular color label."). *Sorge* also specifically states that:

> The same type of information can be encoded in molecular weight 'blocks' of colors or other tags that are in multiples of four... [C]ertain molecular weight ranges or 'gaps' are reserved for post-digestion analysis. The general concept is that a small set of independently discernible tags can be used to trace the alteration in size or molecular weight of a large number of DNA fragments cleaved...

Id. (emphasis added). Thus, the fragments and tags of *Sorge* differ from the mixtures of the independent claims in at least two important ways.

First, claims 1, 2, 7, 12, and 81-83 each recite " any given oligonucleotide sequence in the mixture is attached to preferably a single tag with a discrete molecular weight." The tags of the claims are not " blocks of colors or other tags that are in multiples of four," as described by *Sorge*. Second, the tags of the claims are not limited to those that simply " trace the alteration in size or molecular weight... of DNA fragments," as recited by *Sorge*. Rather, each tag of the instant claims has a discrete molecular weight. Therefore, *Sorge* does not remedy the deficiencies of *Southern* for at least these reasons.

In the Advisory Action mailed November 8, 2005, the Examiner rebuts Applicants foregoing arguments by stating that " the tags with different molecular mass taught by *Sorge*

does read on the tags with discrete molecular weight as claimed in the instant claims. *Advisory Action* at Continuation Sheet. Applicants disagree. Tags with different molecular mass that are " blocks of colors" or are used in " groups in multiples of fours" in order to be effective, as disclosed by *Sorge*, do not render obvious tags with discrete molecular weight, as recited in independent claims. These are different tags, the tags of the claims of which are non-obvious in view of *Sorge*.

In summary, a *prima facie* for obviousness has not been made against Applicants' claims 1, 2, 7, 12, and 81-83. Therefore, Applicants respectfully submit that each of these claims is patentable over *Southern* and *Sorge* and that the rejection of these claims should be withdrawn.

Because the independent claims are allowable, then for at least this reason, their respective dependent claims 3-6, 8-11, 13, 15-17, and 74-80 are also allowable. There may be other reasons as well why the dependent claims are allowable. For example, claim 74 recites "a kit ... comprising: a. the mixture or set of sub-mixtures of claim 1; and b. an enzyme...." Neither *Southern* nor *Sorge* teach or suggest providing a kit that includes the recited mixture or set of sub-mixtures in addition to an enzyme.

(b) Rejection of Claims 1, 3-6, and 74-80 over *Brenner* in view of *Sorge*

Claims 1, 3-6, and 74-80 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over *Brenner* (" *Brenner*," U.S. Pat. No. 5,654,413) in view of *Sorge*. Applicants respectfully traverse this rejection.

In particular, the Office Action alleges that " Brenner teaches a composition (mixture) of claims 1, 3-5, comprising X-mer precursor having a minimum length of 3 nucleotides.., wherein the mixture the mixture (sic) has at least complexity of at least 56/N, wherein N

represents the number of distinct X-mers..." *Office Action* at 5. Applicants disagree. All portions of *Brenner* relied on by the Office have been carefully studied, and they all refer to " an oligonucleotide tag." *See, e.g., Brenner* at col. 3, lines 15-17 (" An oligonucleotide tag of the invention consists of a plurality of subunits, each subunit consisting of an oligonucleotide of 3 to 6 nucleotides in length.") (emphasis added). In contrast, the independent claims recite " X-mer precursors" and " wherein each tag is covalently linked to at least one X-mer precursor" (emaphasis added), thus specifically reciting that the X-mer precursor and the tag are not one and the same species. While Applicants understand that limitations/features of the specification are not to be imported into the claims, the elements of the claims should be interpreted in light of the specification. In the instant case, the specification defines both a tag and an X-mer precursor. Reference to the specification is helpful and appropriate in this instance, where Applicants have acted as their own lexicographer:

> A tag which is useful in the present invention possesses several attributes:
> 1) A tag is distinguishable from all other tags, preferably by mass spectrometry.
> 2) The tag is capable of being detected when present at 10^{-22} to 10^{-6} moles.
> 3) The tag possesses a chemical handle through which it can be attached to a nucleotide or nucleic acid which the tag is intended to identify, preferably uniquely, but not necessarily. The attachment may be made directly to a nucleic acid, or preferably indirectly through a "linker" group, preferably a cleavable linker.
> 4) The tag is chemically stable toward all manipulations to which it is subjected, including attachment and cleavage from the nucleic acid molecule, and any manipulations of the nucleic acid molecule while the tag is attached to it.
> 5) The tag does not significantly interfere with the manipulations performed on the nucleic acid molecule while the tag is attached to it. For instance, if the tag is attached to an oligonucleotide, the tag must not significantly interfere with any hybridization or enzymatic reactions (e.g., PCR sequencing reactions) performed on the oligonucleotide.

Specification at 34, lines 4-18. In contrast, the X-mer precursors are described in the specification as follows:

> The oligonucleotide precursor (X-mer precursor) reagents of the invention are mixtures of natural X-mer precursors, mass-modified X-mer precursors, or natural and mass-modified X-mer precursors having a minimum length of 3 nucleotides....

Id. at 28, lines 23-25. Thus, the Office has taken the tags of Brenner and used them to reject the claims based on the X-mer precursors of the claims. *Sorge* does not remedy this deficiency of *Brenner*. For at least this reason, the combination of *Sorge* and *Brenner* does not teach or suggest all features of independent claim 1.

In addition, the Office admits that *Brenner* does " not specifically teach any oligonucleotide sequence in the mixture is attached to preferably a single tag with a discrete molecular weight, tags distinguishable by mass spectrometry." *Office Action* at 6, lines 5-7. *Sorge* does not remedy these deficiencies of the *Brenner* reference either. The fragments and tags of *Sorge* differ from the mixtures in the independent claims for at least two reasons stated above with respect to its combination with the *Southern* reference. For at least the same reasons, the combination of *Brenner* and *Sorge* do not teach or suggest all elements of independent claim 1.

In the Advisory Action mailed November 8, 2005, the Examiner rebuts Applicants foregoing arguments by stating that " the claim limitations are broader in scope than that recited in the specification." *Advisory Action* at Continuation Sheet. Applicants disagree. When an applicant chooses to be its own lexicographer and specifically defines claim terms in the specification, then the claims are to be compared to the prior art based on the defined claim terms. In the instant case, the defined claim terms are not obvious in view of the *Brenner* and *Sorge* for the reasons discussed above.

In summary, a *prima facie* for obviousness has not been made against Applicants' claim 1. Therefore, Applicants respectfully submit that this claim is patentable over *Brenner* and *Sorge* and that the rejection of these claims should be withdrawn.

Because independent claim is allowable, then for at least this reason, its dependent claims 3-6, and 74-80 are also allowable. There may be other reasons as well why the dependent claims are allowable. For example, claim 74 recites "a kit ... comprising: a. the mixture or set of sub-mixtures of claim 1; and b. an enzyme...." Neither *Brenner* nor *Sorge* teach or suggest providing a kit that includes the recited mixture or set of sub-mixtures in addition to an enzyme.

CONCLUSION

Based upon the foregoing discussion, Applicants respectfully requests that the Examiner's final rejection of claims 1-17 and 74-83 be overruled and withdrawn by the Board, and that the application be allowed to issue as a patent with all pending claims.

Respectfully submitted,

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VIII. CLAIMS - APPENDIX

1. (Previously presented) A mixture or set of sub-mixtures comprising X-mer precursors,

wherein the X-mer precursors have a minimum length of 3 nucleotides;

wherein the mixture has a minimum mixture coverage complexity of at least 56/N or wherein the set of sub-mixtures has a composite mixture coverage complexity of at least 56/N, wherein N represents the number of distinct X-mer precursors in the mixture;

wherein each sub-mixture in said set has a reduced mixture coverage complexity as compared with the composite mixture coverage complexity;

wherein each sub-mixture comprises a plurality of X-mer precursors;

wherein said length is selected independently for each X-mer precursor; and

wherein the mixture or set of sub-mixtures further comprises a set of tags that are distinguishable by mass spectrometry, wherein each tag is covalently linked to at least one X-mer precursor through a cleavable linker such that any given oligonucleotide sequence in the mixture is attached to preferably a single tag with a discrete molecular weight.

2. (Previously presented) A mixture or set of sub-mixtures comprising X-mer precursors, wherein said X-mer precursors have a minimum length of 3 nucleotides;

wherein said mixture has a minimum mixture coverage complexity of at least 56/N or wherein said set of sub-mixtures has a composite mixture coverage complexity of at least 56/N, wherein N represents the number of distinct X-mer precursors in the mixture;

wherein each sub-mixture in said set has a reduced mixture coverage complexity as compared with the composite mixture coverage complexity;

wherein each sub-mixture further comprises a plurality of X-mer precursors;

wherein said length is selected independently for each X-mer precursor;

wherein the mixture or set of sub-mixtures further comprises a set of tags wherein each tag is covalently linked to at least one X-mer precursor through a cleavable linker such that any given oligonucleotide sequence in the mixture is attached to preferably a single tag with a discrete molecular weight; and

wherein said X-mer precursors have a determined isotopic composition.

3. (Original) The mixture or set of sub-mixtures of claim 1 or 2 wherein said mixture has a mixture coverage complexity of at least about 1/2 when said mixture contains at least 128 discrete X-mers, or wherein said set of sub-mixtures has a composite mixture coverage complexity of at least about 1/2 when said set of sub-mixtures contains at least 128 discrete X-mers.

4. (Original) The mixture or set of sub-mixtures of claim 1 or 2, wherein said mixture has a mixture coverage complexity of at least about 1/4 when said mixture contains at least 256 discrete X-mers, or wherein said set of sub-mixtures has a composite mixture coverage complexity of at least about 1/4 when said set of sub-mixtures contains at least 256 discrete X-mers.

5. (Original) The mixture or set of sub-mixtures of claim 1 or 2, wherein said mixture has a mixture coverage complexity of at least about 1/8 when said mixture contains at least 512 discrete X-mers, or wherein said set of sub-mixtures has a composite mixture coverage complexity of at least about 1/8 when said set of sub-mixtures contains at least 512 discrete X-mers.

6. (Original) The mixture or set of sub-mixtures of claim 1 or 2, wherein nucleotide sequences of the precursors of said mixture or set of sub-mixtures are known.

7. (Previously presented) A mixture or set of sub-mixtures comprising X-mer precursors,

wherein the X-mer precursors have a minimum length of 3 nucleotides;

wherein the mixture has a minimum mixture coverage complexity of at least 56/N or wherein the set of sub-mixtures has a composite mixture coverage complexity of at least 56/N, wherein N represents the number of distinct X-mer precursors in the mixture;

wherein each sub-mixture in said set has a reduced mixture coverage complexity as compared with the composite mixture coverage complexity;

wherein each sub-mixture comprises a plurality of X-mer precursors;

wherein said length is selected independently for each X-mer precursor;

wherein the mixture or set of sub-mixtures further comprises a set of tags wherein

each tag is covalently linked to at least one X-mer precursor through a cleavable linker such that any given oligonucleotide sequence in the mixture is attached to preferably a single tag with a discrete molecular weight; and

wherein a number of tags in the set of tags distinguishable by mass spectrometry after cleavage of the linkers is between approximately 10-100,000.

8. (Previously Amended) The mixture or set of sub-mixtures of claim 7 or 81, wherein a number of tags in the set of tags distinguishable by mass spectrometry after cleavage of the linkers is between approximately 20-20,000.

9. (Previously Amended) The mixture or set of sub-mixtures of claim 7 or 81, wherein a number of tags in the set of tags distinguishable by mass spectrometry after cleavage of the linkers is between approximately 20-10,000.

10. (Previously Amended) The mixture or set of sub-mixtures of claim 7 or 81, wherein a number of tags in the set of tags distinguishable by mass spectrometry after cleavage of the linkers is between approximately 20-5,000.

11. (Previously Amended) The mixture or set of sub-mixtures of claim 7 or 81, wherein a number of tags in the set of tags distinguishable by mass spectrometry after cleavage of the linkers is between approximately 50-1000.

12. (Previously presented) A mixture or set of sub-mixtures comprising X-mer precursors,

wherein the X-mer precursors have a minimum length of 3 nucleotides;

wherein the mixture has a minimum mixture coverage complexity of at least 56/N or wherein the set of sub-mixtures has a composite mixture coverage complexity of at least 56/N, wherein N represents the number of distinct X-mer precursors in the mixture;

wherein each sub-mixture in said set has a reduced mixture coverage complexity as compared with the composite mixture coverage complexity;

wherein each sub-mixture comprises a plurality of X-mer precursors;

wherein said length is selected independently for each X-mer precursor;

wherein the mixture or set of sub-mixtures further comprises a set of tags wherein each tag is covalently linked to at least one X-mer precursor through a cleavable linker such that any given oligonucleotide sequence in the mixture is attached to preferably a single tag with a discrete molecular weight; and

wherein a number of tags in the set of tags distinguishable by mass spectrometry after cleavage of the linkers is greater than a mass number complexity (MNC) of a natural equivalent of the mixture or set of sub-mixtures, wherein the natural equivalent of the X-mer precursors are extended by one nucleotide, and wherein the number of tags in the set of tags is less than or equal to a number of X-mer precursors in the mixture or set of sub-mixtures.

13. (Previously Amended) The mixture or set of sub-mixtures of claim 12 or 82, wherein a number of tags in the set of tags distinguishable by mass spectrometry after cleavage of the linkers is greater than 75% of a mass number complexity (MNC) of a natural equivalent of mixture or set of sub-mixtures, wherein the natural equivalent of the X-mer precursors are extended by one nucleotide, and wherein the number of tags in the set of tags is less than or equal to a number of X-mer precursors in the mixture or set of sub-mixtures.

14. (Previously presented) A mixture or set of sub-mixtures comprising X-mer precursors, wherein the X-mer precursors have a minimum length of 3 nucleotides;

wherein the mixture has a minimum mixture coverage complexity of at least 56/N or wherein the set of sub-mixtures has a composite mixture coverage complexity of at least 56/N, wherein N represents the number of distinct X-mer precursors in the mixture;

wherein each sub-mixture in said set has a reduced mixture coverage complexity as compared with the composite mixture coverage complexity;

wherein each sub-mixture comprises a plurality of X-mer precursors;

wherein said length is selected independently for each X-mer precursor;

wherein the mixture or set of sub-mixtures further comprises a set of tags wherein each tag is covalently linked to at least one X-mer precursor through a cleavable linker such that any given oligonucleotide sequence in the mixture is attached to preferably a single tag with a discrete molecular weight; and

wherein a number of tags in the set of tags distinguishable by mass spectrometry after cleavage of the linkers is at least 0.5% of a number of X-mer precursors in the mixture or set of sub-mixtures, and less than or equal to the number of X-mer precursors in the mixture or set of sub-mixtures.

15. (Previously Amended) The mixture or set of sub-mixtures of claim 14 or 83, wherein a number of tags in the set of tags distinguishable by mass spectrometry after cleavage of the linkers is at least 1% of a number of X-mer precursors in the mixture or set of sub-mixtures, and less than or equal to the number of X-mer precursors in the mixture or set of sub-mixtures.

16. (Previously Amended) The mixture or set of sub-mixtures of claim 14 or 83, wherein a number of tags in the set of tags distinguishable by mass spectrometry after cleavage of the linkers is at least 10% of a number of X-mer precursors in the mixture or set of sub-mixtures, and less than or equal to the number of X-mer precursors in the mixture or set of sub-mixtures.

17. (Previously Amended) The mixture or set of sub-mixtures of claim 14 or 83, wherein a number of tags in the set of tags distinguishable by mass spectrometry after cleavage of the linkers is at least 25% of a number of X-mer precursors in the mixture or set of sub-mixtures, and less than or equal to the number of X-mer precursors in the mixture or set of sub-mixtures.

18-73. (Cancelled)

74. (Original) A kit for carrying out a method of analyzing a target nucleic acid sequence, comprising:

a. the mixture or the set of sub-mixtures of claim 1; and

b. an enzyme having a nucleotide polymerase activity.

75. (Original) The kit of claim 74, further comprising a multiplicity of nucleotides selected from the group consisting of natural chain-terminating triphosphates and modified chain-terminating triphosphates.

76. (Original) The kit of claim 74, further comprising chain-terminating nucleotides with an affinity label for purification of nucleic acids.

77. (Original) A kit for carrying out a method of analyzing a target nucleic acid sequence comprising:

a. the mixture or the set of sub-mixtures of claim 1; and

b. a DNA ligase.

78. (Original) A kit for carrying a method of analyzing a target nucleic acid sequence, comprising:

a. the mixture or the set of sub-mixtures of claim 1; and

b. a condensing agent.

79. (Original) A kit for carrying out a method of analyzing a target nucleic acid sequence having a 3'-end and a 5'-end, comprising:

a. the mixture or the set of sub-mixtures of claim 1;

b. a DNA ligase; and

c. an array comprising:

(a) a surface; and

(b) a multiplicity of nucleic acid sequence probes comprising:

(i) a nucleic acid attached to said surface, wherein the nucleic acid has a terminal 3'-hydroxyl end and wherein the 5' end is directly or indirectly attached to said surface.

80. (Original) A kit for carrying out a method of analyzing a target nucleic acid sequence having a 3'-end and a 5'-end, comprising:

a. the mixture or the set of sub-mixtures of claim 1;

b. a condensing agent; and

c. an array comprising:

(a) a surface; and

(b) a multiplicity of nucleic acid sequence probes comprising:

(i) a nucleic acid attached to said surface, wherein the nucleic acid has a terminal 3'-hydroxyl end and wherein the 5' end is directly or indirectly attached to said surface.

81. (Previously presented) A mixture or set of sub-mixtures comprising X-mer precursors,

wherein the X-mer precursors have a minimum length of 3 nucleotides;

wherein the mixture has a minimum mixture coverage complexity of at least 56/N or wherein the set of sub-mixtures has a composite mixture coverage complexity of at least 56/N, wherein N represents the number of distinct X-mer precursors in the mixture;

wherein each sub-mixture in said set has a reduced mixture coverage complexity as compared with the composite mixture coverage complexity;

wherein each sub-mixture comprises a plurality of X-mer precursors;

wherein said length is selected independently for each X-mer precursor;

wherein the mixture or set of sub-mixtures further comprises a set of tags wherein each tag is covalently linked to at least one X-mer precursor through a cleavable linker such that any given oligonucleotide sequence in the mixture is attached to preferably a single tag with a discrete molecular weight;

wherein said X-mer precursors have a determined isotopic composition; and

wherein a number of tags in the set of tags distinguishable by mass spectrometry after cleavage of the linkers is between approximately 10-1,000,000.

82. (Previously presented) A mixture or set of sub-mixtures comprising X-mer precursors, wherein the X-mer precursors have a minimum length of 3 nucleotides;

wherein the mixture has a minimum mixture coverage complexity of at least 56/N or wherein the set of sub-mixtures has a composite mixture coverage complexity of at least 56/N, wherein N represents the number of distinct X-mer precursors in the mixture;

wherein each sub-mixture in said set has a reduced mixture coverage complexity as

compared with the composite mixture coverage complexity;

wherein each sub-mixture comprises a plurality of X-mer precursors;

wherein said length is selected independently for each X-mer precursor;

wherein the mixture or set of sub-mixtures further comprises a set of tags wherein each tag is covalently linked to at least one X-mer precursor through a cleavable linker such that any given oligonucleotide sequence in the mixture is attached to preferably a single tag with a discrete molecular weight;

wherein said X-mer precursors have a determined isotopic composition; and

wherein a number of tags in the set of tags distinguishable by mass spectrometry after cleavage of the linkers is greater than a mass number complexity (MNC) of a natural equivalent of the mixture or set of sub-mixtures, wherein the natural equivalent of the X-mer precursors are extended by one nucleotide, and wherein the number of tags in the set of tags is less than or equal to a number of X-mer precursors in the mixture or set of sub-mixtures.

83. (Previously presented) A mixture or set of sub-mixtures comprising X-mer precursors,

wherein the X-mer precursors have a minimum length of 3 nucleotides;

wherein the mixture has a minimum mixture coverage complexity of at least 56/N or wherein the set of sub-mixtures has a composite mixture coverage complexity of at least 56/N, wherein N represents the number of distinct X-mer precursors in the mixture;

wherein each sub-mixture in said set has a reduced mixture coverage complexity as compared with the composite mixture coverage complexity;

wherein each sub-mixture comprises a plurality of X-mer precursors;

wherein said length is selected independently for each X-mer precursor;

wherein the mixture or set of sub-mixtures further comprises a set of tags wherein each tag is covalently linked to at least one X-mer precursor through a cleavable linker such that any given oligonucleotide sequence in the mixture is attached to preferably a single tag with a discrete molecular weight; and

wherein a number of tags in the set of tags distinguishable by mass spectrometry after cleavage of the linkers is at least 0.5% of a number of X-mer precursors in the

mixture or set of sub-mixtures, and less than or equal to the number of X-mer precursors in the mixture or set of sub-mixtures.

IX. EVIDENCE - APPENDIX

None.

IX. RELATED PROCEEDINGS- APPENDIX

None.